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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,809	10/17/2003	Bernd Nickel	017094-0306034	8786

909 7590 06/22/2007

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	**PAPER NUMBER**
1614	

MAIL DATE	DELIVERY MODE
06/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/686,809	NICKEL ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-21 and 23-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-21 and 23-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 1 SHEET
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 14-21 & 23-30 ARE PRESENTED FOR EXAMINATION

Applicants' amendment filed 4/6/2007 has been received and entered into the application. Accordingly, claims 14-15, 19-21, 23, 25-26 and 29 have been amended, claim 22 has been cancelled and claim 30 has been added.

In view of the above amendments, the objection to the disclosure and the objections claims 20, 23, 25 and 26 have been overcome and thus are *withdrawn*. Also, the amendments and Applicants' remarks have overcome the rejections not reiterated herein from the previous office action. Such rejections are hereby withdrawn. The following rejections are either reiterated or newly applied and constitute the totality of issues remaining in the present application.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. § 119(a)-(d), which papers have been placed of record in the file.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-21 and 23-29 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for treating multidrug-resistant tumors, inhibiting angiogenesis or metastasis with a sub-genus of the claimed compounds, does not reasonably provide enablement for treating multidrug-resistant tumors, inhibiting angiogenesis or metastasis

with the full scope of the claimed compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

Applicants' arguments have been fully considered and are persuasive in part. With respect to the treatment of multidrug-resistant tumors, inhibition of angiogenesis and inhibition of metastasis, the Examiner is persuaded that D-24851 is enabled for the full scope of the claimed invention. For example, Applicants' Exhibit A, a journal article dated 2001, demonstrates that D-24851 inhibits the growth of multiple tumor cell lines (*e.g.*, ovarian, prostate, cervical, colon, lung, pancreatic, brain, breast and leukemic). In addition, D-24851 was shown to inhibit the growth of different drug-resistant tumor cell lines (*e.g.*, leukemic, breast and colon) that were multidrug resistant, resistant to cisplatin, resistant to 5-FU or resistant to raltitrexed. Accordingly, D-24851 and related compounds are enabled for the full scope of the claimed invention because the skilled artisan would reasonably expect D-24851 and structurally related compounds to be effective in treating multidrug-resistant tumors, inhibiting angiogenesis and inhibiting metastasis. However, the instant claims recite a broad genus of compounds having multiple substituents. Based on the direction and guidance provided in the specification, it would take undue experimentation to determine exactly which compounds, other than those structurally related to D-24851, would be effective in treating multidrug-resistant tumors, inhibiting angiogenesis and inhibiting metastasis.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.

In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to the treatment of multidrug-resistant tumors, inhibition of angiogenesis and inhibition of metastasis with a broad genus of structurally diverse compounds.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing

specific avian recombinant virus vaccine was uncertain). The art of treating cancer, particularly in humans, is extremely unpredictable, particularly in the case of a broad genus of compounds being used to treat any and all cancers.

2. The breadth of the claims

The claims vary in breadth; some (such as claim 14) vary broadly, reciting the treatment of tumors with a broad genus of compounds. Others, such as claims 19 and 29, are narrower, reciting specific species of the claimed genus of compounds. All, however, are extremely broad insofar as they disclose the general treatment of resistant and metastasizing tumors with the same compounds.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat all of the various tumors claimed, particularly in humans. The direction concerning treating cancer is found in the specification at pages 9-12, which provides a cellular assay and an *in vivo* assay for determining the cell growth inhibitory effect of the claimed compounds. The working examples are limited to: 1) the *in vitro* cytotoxic effects of one compound, D-24851, on one multidrug resistant leukemia cell line; 2) the inhibition of metastasis of MO4 fibrosarcoma cells by D-24851; and 3) the antiangiogenic effect of D-24851.[2] Applicants describe formulations at

[2] Examiner notes that leukemia is a blood-borne cancer, not a "tumor" *per se*.

page 8. Doses required to practice their invention are described at pages 11-12. A 25-fold range of doses is recommended for oral administration (*e.g.*, 20 mg to 500 mg/kg). Since only one compound as instantly claimed has ever been demonstrated to treat any human cancer, how is the skilled physician to know what dose to use for each of these pathologically different cancers and structurally diverse compounds? There are no guidelines for determining the doses needed to treat a carcinoma *vs.* a myeloid disorder *vs.* adenoma. Are the identical doses to be used for treating these unrelated cancers? There is both an *in vitro* cellular assay and an *in vivo* assay described in pages 9-12 and it is unclear if these assays correlate to all of the cancers encompassed by the claims. As noted *supra*, in view of Applicants' disclosure and the art related to the claimed invention, the skilled artisan would reasonably expect that compounds structurally related to D-24851 would be effective to treat the claimed conditions and tumors. However, it is not predictable that the full scope of the claimed compounds will have the same effect as D-24851.

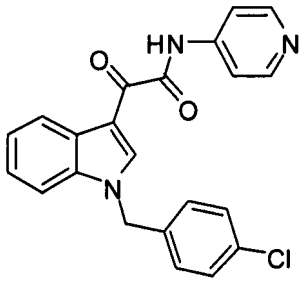
4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed genus of compounds could be predictably used as a treatment for all multidrug-resistant tumors, angiogenesis and metastasis as inferred in the claims and contemplated by the specification.

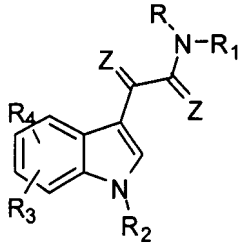
Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is

granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because D-24851 inhibits multidrug-resistant tumor growth, angiogenesis and metastasis, all compounds of formula I as recited in claim 14 must therefore, *a priori*, be useful in the treatment of multidrug-resistant tumor growth, angiogenesis and metastasis. However, the claims encompass a multitude of compounds having a plethora of chemically and biologically distinct substituents. Applicants synthesized and tested one compound, D-24851 (see Figures 1-9).



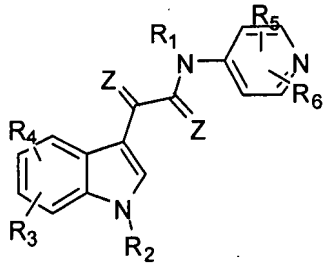
D-24851



Formula (I)

It is evident that a very small percentage of the claimed compounds were actually synthesized and tested by Applicants. For example, no compounds having an R substituent other than hydrogen were tested. It is not predictable that if R were, for example, a benzyl group as encompassed by the claims that such a compound would have similar activity to that of D-24851. Similarly, D-24851 has a *pyridine* group at R_1. If R_1 were anything other than a pyridine or substituted pyridine group, would similar activity to D-24851 be expected? R_2 is a substituted benzyl group in the compounds tested by Applicants. However, the claims encompass compounds wherein R_2 can anything from hydrogen to a substituted C_1-C_6 alkyl group.

Given the extremely diverse compounds encompassed by the claims and the limited examples provided in the specification, the skilled artisan cannot predict what structural features (other than those of the compounds actually synthesized) are important for activity. In other words, the structure activity relationship demonstrated in the examples is limited to a very small sub-genus of compounds. Favorable consideration would be given to claims limited to compounds structurally related to D-24851 (*e.g.*, compounds of the genus shown below, wherein R_1 is hydrogen, R_2 is a benzyl group optionally substituted as defined in claim 14, and R_3, R_4, R_5, R_6 and Z are defined as in claim 14).



Determining if any particular claimed compound would treat any particular cancerous disease state would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants. As noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The following double patenting rejections are maintained for the reasons of record. Applicants did not address these rejections in the response filed 4/6/2007.

U.S. Patent No. 6,232,327

Claims 14-21 & 23-30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,232,327. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant claims and the claims of the '327 patent are drawn to the treatment of tumors with the same compounds. One skilled in the art would recognize that "resistant tumors", "metastasis" and "angiogenesis" are all within the scope of the '327 patent. Further, the "comprising" language of the '327 patent allows for the administration of other compounds, including the instantly claimed antitumor agents.

U.S. Patent No. 6,693,119

Claims 14-21 & 23-30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-6, 10 and 12 of U.S. Patent No. 6,693,119. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant claims and the claims of the '119 patent are drawn to the treatment of tumors with the same compounds. Further, the "comprising" language of the '119 patent allows for the administration of other compounds, including the instantly claimed antitumor agents.

U.S. Non-Provisional Application No. 10/309,204

Claims 14, 18, 19 and 23-30 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11-14 and 16-23 of copending Application No. 10/309,204. Although the conflicting claims are not identical, they

are not patentably distinct from each other because the instant claims read on the claims of the '204 application when the compounds are used to treat the cancers recited in '204. For example, one skilled in the art would recognize that treating a prostate carcinoma (recited in the claims of '204) will naturally result in the treatment of metastasis and angiogenesis as instantly claimed. Further, the "comprising" language of the '204 application allows for the administration of other compounds, including the instantly claimed antitumor agents.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

June 15, 2007

Phyllis Spivack

PHYLLIS SPIVACK
PRIMARY EXAMINER

6/15/07